



National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

DATE: August 27, 2009
FROM: L. Austin Doyle, M.D., Senior Investigator, Investigational Drug Branch, CTEP, DCTD, NCI
SUBJECT: CCI-779 (Temsirolimus, Torisel®) IND Safety Report, AE# 1795312
TO: Investigators Using CCI-779 (Temsirolimus, Torisel®) (NSC 683864)

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies conducted under a U.S. IND to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. Please find attached a copy of an IND Safety Report recently submitted to the FDA for the CTEP-sponsored investigational agent temsirolimus.

The following must be completed by all investigators using temsirolimus under NCI IND 61010

- Send a copy of the IND Safety Report to your Institutional Review Board (IRB) according to your local IRB's policies and procedures.
- File a copy of the IND Safety Report in your protocol file.

If your study is not covered under IND 61010, it is strongly recommended that you follow the instructions above.

Please note that for Cooperative Group studies, the Cooperative Group Operations Office will provide instructions for IRB submissions, any patient notifications, etc.

Based on CTEP's assessment of the current information in light of previous experience with temsirolimus, there does not appear to be a change in the risk-benefit ratio for temsirolimus, therefore, CTEP is not requiring a protocol amendment at this time.

Please continue to report events according to the adverse event reporting guidelines in your protocol(s).

The attached Adverse Events Assessment describes the adverse event(s) (synopsis provided below), relevant previous experience under these INDs and/or NSCs, and the total number of patients enrolled in trials under these INDs and/or NSCs.

A 68-year-old male with mantle cell lymphoma developed grade 3 left ventricular systolic dysfunction while on a phase 2 trial utilizing the investigational agent temsirolimus.

ADVERSE EVENTS ASSESSMENT

IND 61010 NSC 683864 CCI-779 (temsirolimus, Torisel®)	ADVERSE EXPERIENCE REPORT NO. IND Safety Report: #1 Event: Gr. 3: Left ventricular systolic dysfunction
AE: 1795312	Protocol: N038H

The patient is a 68-year-old male with mantle cell lymphoma who developed left ventricular systolic dysfunction (congestive heart failure) while on a phase 2 trial utilizing the investigational agent temsirolimus in combination with rituximab. He began the first course of the investigational therapy on June 16, 2008, receiving temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22, rituximab 375 mg/m² IV at an initial rate of 50 mg/hour increasing by 50 mg/hour every 30 minutes to a maximum of 400 mg/hour on Day 1, then rituximab 375 mg/m² IV at an initial rate of 100 mg/hour increasing by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour on Days 8, 15, and 22 in Cycle 1. For Cycle 2 and beyond, the patient received temsirolimus 25 mg IV over 30 minutes on Days 1, 8, 15, and 22 and rituximab 375 mg/m² IV at an initial rate of 100 mg/hour increasing by 100 mg/hour every 30 minutes to a maximum of 400 mg/hour on Day 1 of Cycles 3, 5, 7, 9 and 11 only, every 4 weeks. The patient received his last dose of temsirolimus on February 9, 2009 (Cycle 9, Day 15), and the last dose of rituximab on January 26, 2009 (Cycle 9, Day 1).

The patient was initially diagnosed with mantle cell lymphoma in March 2008, and is status post chemotherapy and an autologous stem cell transplant. He began the investigational therapy on June 16, 2008. On February 9, 2009 (Cycle 9, Day 15) the patient was placed into an event monitoring phase due to toxicities.

On February 24, 2009 (Cycle 9, Day 30), the patient presented to the clinic to remove his chemotherapy port when he was found to be tachycardic with a heart rate in the 140s. The patient, who denied chest pain, was admitted to the hospital for paroxysmal atrial fibrillation and hypoxia stating that for the past month he had been experiencing shortness of breath, orthopnea, paroxysmal nocturnal dyspnea, occasional cough from clear phlegm, and wheezing. He was pleasant and fully oriented, had a temperature of 97.6° F, respiration of 20 breaths per minute, pulse of 133 bpm, blood pressure of 109/78 mmHg, and an oxygen saturation of 96% on room air. He had a rapid but regular heart rate and grade 1-2 pitting edema bilaterally. The ECG on admission showed sinus tachycardia although it is noted that a previous ECG showed atrial fibrillation. He was started on Cardizem®, first orally then via IV drip.

On February 25, 2009, a transthoracic echocardiogram revealed mild concentric left ventricular hypertrophy with an ejection fraction (EF) of 25-30%, moderate to severe global hypokinesis of the left ventricle, mild to moderate mitral regurgitation, mild tricuspid regurgitation, right ventricular pressures of 35-40 mmHg, and a small pericardial effusion. The patient's ECG now revealed atrial fibrillation with a rapid ventricular response with nonspecific ST-T wave changes. A CT scan of the chest showed no evidence of pulmonary emboli, moderate dependent bilateral pleural effusions and adjacent lung atelectasis, pulmonary edema, and peribronchial cuffing. A consulting cardiologist added digoxin, an ACE inhibitor, and heparin in preparation for a transesophageal echocardiogram (TEE) and possible cardioversion. The next day a TEE revealed a left atrial thrombus and no pericardial effusion. Cardioversion was held.

On February 27, 2009, a cardiac catheterization showed double vessel disease with obstruction in the right coronary artery and distal left anterior descending artery, and globally decreased left ventricular function out of proportion to coronary disease suggesting likely non-ischemic cardiomyopathy; it also revealed severe global hypokinesis and an EF of 30%. With these new cardiac findings, the question of

prior anthracycline therapy was raised. The remainder of the patient's hospital course was focused on treating his congestive heart failure, atrial fibrillation, and coronary artery disease. In addition to the aforementioned medications, he was given furosemide, low dose aspirin, a statin and a beta-blocker. The patient's weight decreased from 91 kg on the day of admission to 83 kg on the day of discharge. He was discharged home on March 2, 2009, on multiple medications with instructions for follow-up.

The patient's past medical/surgical history is significant for a chemotherapy port-associated deep vein thrombosis, a 100 pack-year smoking history, and right ankle surgery. His mother died of gallbladder cancer, and his father died of lymphoma. Medications taken at the time of the event included Coumadin®.

There have been 10 other cases of left ventricular systolic dysfunction reported to the NCI as a serious adverse event through AdEERS under the temsirolimus NSC and/or IND as shown in the table below.


Adverse Event	Grade	Attribution
Left ventricular systolic dysfunction (n=10)	3 2	3 Unrelated, 2 Unlikely, 4 Possible 1 Unlikely

To date, a total of 1,720 patients have been enrolled in NCI-sponsored clinical trials under the temsirolimus IND and/or NSC.

In this case, it is felt that a possible relationship exists between the event and the investigational agent.

	Left ventricular systolic dysfunction
CCI-779 (temsirolimus, Torisel)	Possible
Rituximab	Unrelated
Mantle cell lymphoma	Unrelated

Date: 8/28/09

Signature: 
 L. Austin Doyle, M.D.
 (IDB Monitor for temsirolimus)

If this assessment is changed, we will notify your office.

cc: Rafael E. Curiel, Ph.D.
WASDTRI@wyeth.com
 Wyeth Pharmaceuticals, Inc.